

Cortisol levels, IFN- γ and TNF- α in ischemic stroke patients

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Abstract

Stress is one cause of stroke. Stroke is a disease that needs attention, given the increasing prevalence and cause of morbidity and mortality of patients. Model home care is an approach to holistic nursing care at home that emphasizes the intervention of bio-psycho-social-spiritual. This study aims to determine the effect of differences in the levels of cortisol, IFN- γ and TNF- α before and after intervention between groups holistic model of home care and group home care. This research study design experiments with a model of the pre-post test group design and subjects were measured biological responses such as cortisol, IFN- γ and TNF- α . The sample in this study were all patients with ischemic stroke who had been allowed to go home after hospitalization in room Seruni A Hospital Dr. Soetomo in 2009 and settled in the city of Surabaya consisting of 40 patients. The results showed differences in the levels of cortisol, IFN- γ and TNF- α in patients after ischemic stroke before the homecare holistic intervention. There are differences in excess cortisol, IFN- γ and TNF- α in patients with ischemic stroke who received care home model of care with a model of home care holistic.

Keywords : Cortisol, IFN- γ , TNF- α

1. Introduction

Stress is one cause of stroke. Stroke is a disease that needs attention, given the increasing prevalence and cause of morbidity and mortality of patients. In Indonesia, stroke is the number three deadly disease after heart disease and cancer. In fact, according to the 2004 survey, stroke is the number one killer in the hospital. Governments all over Indonesia. It is estimated that the number of stroke patients reached 212 thousand people, the sheer number of stroke patients is increasing every year, not only attacks the elderly, but also experienced by those who are young and productive. It is estimated that each year 500,000 people affected by stroke. About 2.5% or 125,000 people have died and the rest mild or severe disability. Their disability due to stroke clothing, not just a burden on the family, but also the general public burden (Yastroki, 2007).

Approach medicopsychological stress is the basic paradigm of psychoneuroimmunology. These types of stressors cause non-specific interference in the system biological. Hans Selye in Putra (1999) says that the response against stressors may be manifested as stress biological. Stress as a biological response. It is conformed to the idea Selye that stress focuses on a person's reaction to stressors and describe stress as a response.

Patients who experience prolonged stress based on the concept of psychoneuroimmunology, via astrocytes in cortical and amygdala in the limbic system affects the hypothalamus. Then the pituitary will produce CRF, ie the basophilic cells. The basophilic cells will express ACTH (adrenal cortico tropic hormone) which ultimately can affect the adrenal cortex gland cells fasciculata zone, this gland will produce cortisol that are immunosuppressive. If the stress experienced by patients is very high, the adrenal glands will produce cortisol in large quantities so as to suppress the immune system (Apasou & Sitkorsy, 1999). Which includes the activity of APC (macrophages); Th-1, CD-4; and plasma cell IFN- γ , IL-2, TNF- α ; IgM and IgG and antibody.

Patients who experience stress or stroke requires treatment and palliative care there is no time limit to when admitted to the hospital so it needs to be treated at home (home care). Meanwhile we do the analysis in Indonesia fact indicates the approach of nursing care home model of care is still focused on the physiological needs (physical) in this case the services provided only to physical health, so that home care is exercised only by the standard of service as in the hospital. Thus the model of nursing home care is given in stroke patients has not been optimal. That situation will get worse if there is a holistic treatment efforts involving multiple parties and better models of care (Depkes, 2002).

This model of home care holistic to provide assurance about the quality of nursing care for patients which provide nursing care in a holistic manner (bio-psycho-social-spiritual). Care biological (physical) is a service provided for the welfare of physical health (Ronaldson, 2000). Biological nursing care can be a home care with the control diet, bowel, skin care, sleep position, sitting, standing, and pemakaina wheelchair. In addition to home care, other things must be considered in pasien stroke is a tool that was in the bathroom, clothes, perlengkapan eating, and other equipment (physiotherapy, bell, trolley). If the two main things that are not observed, then the effects on stroke patients are paralyzed, mental changes, communication disorders, emotional disorders, and loss of sense of taste (Depkes, 2002).

Based on the above proves that there is currently no results prove that after the home care is holistic in ischemic stroke patients may have improved biological response and if the role of home care is holistic in ischemic stroke is not clear, then the understanding of the role of holistic care home can not be utilized for the development of

cerebral infarction prevention, so that disability due to ischemic stroke will remain large. In this regard, it is necessary to study the levels of cortisol, IFN- γ and TNF- α in patients with ischemic stroke.

2. Literature Review

2.1. *The concept of stress and stressors*

Definitions for medikopsikologi and stress learning approach starts with the concept of Selye (1983). Selye describes stress is a condition that dimanifetasikan with specific symptoms that comprise the non-specific changes and biological systems. Stress occurs when a challenge to the stimulus. Stress is done as a generalization and response psikological symptoms are non-specific. Within a few years, the stress as the activation of two neuroendocrine system, anterior pituitary- kortical Adreno system (PAC) and the sympathetic adrenal medulla (Cox, 1995).

Selye (1983) describes the stress response can be significantly associated with physical pathology. This happens when the stressors often happens, of long duration and severe. Paradoxical situation increases when the stress response has evolved gradually adaptively within a short period of time, increasing the ability of humans to respond actively in a noxious environment. However, in the long term this can lead to the disease process.

2.2. *Ischemic stroke*

Stroke occurs when there is an interruption of cerebral blood flow to a part of the brain. Ischemia cause brain energy metabolism with accumulation of calcium ions in the intracellular space, increased levels of lactate, acidosis, and the production of free radicals, resulting in disruption of cellular homeostasis. When the disorder is severe enough, there will be the death of the cell. Total disruption of cerebral blood flow leading to suppression of electrical activity within 12-15 seconds, inhibition of synaptic excitability of cortical neurons after 2-4 minutes, and barriers electrical excitability 4-6 minutes (Love, 1999).

Ischemic stroke has several causes, but the typical caused by emboli further atherothrombotic or interfere with blood flow of the brain (cerebral blood flow, CBF). Under normal circumstances, the CBF is 50-60ml/100g of tissue per minute. Ischemia where CBF occurs when less than 30 ml / 100 g tissue per minute. When where CBF drop below 100 ml / 100 g tissue per minute, there will be a failure of homeostasis, which is followed by a rapid calcium influx, activation of proteases, state and excitotoxic neuronal death (Schneck, 1998). Injury due to reperfusion (reperfusion injury) that ensues can cause free radicals are released, which leads to cell death, Reperfusion also can cause hemorrhagic transformation of infarct tissue bland.

2.2. *Hormones and cytokines that play a role in ischemic stroke*

In the immunological reaction or an inflammatory reaction similar to many substances hormone secreted by T and B lymphocytes as well as by other cells, which function as intercellular signals that regulate local and systemic inflammatory response to external stimuli. Secretion of substances that are restricted as needed. The substance is generally known as cytokines. There are some common characteristics possessed by each cytokine, namely: 1) the secretion of cytokines are generally brief and limit themselves; cytokines never stored as preformed molecules and cytokine synthesis usually begins with the transcription of genes that occur as a result of stimulation; 2) each cytokine normally produced by more than one type of cell, can react to multiple cell types (peliotropik) and have different impacts on different types of targets. On the other hand various types of cytokines have different impacts on the same types of targets; 3) cytokines often affect the synthesis and activity of other cytokines; 4) the activity of cytokines can be local or systemic; 5) cytokines are mediators of the immune response that is very potent and capable of interacting with receptors on the cell surface (Kresno, 2002).

2.3. *Cortisol*

Cortisol is synthesized from cholesterol. Undergo esterification of cholesterol by cholesterol esterase and stored in lipid droplets. The formation of free cholesterol in lipid droplets carried by cholesterol esterase hydrolase. Stimulation by ACTH will result in the activation of cholesterol esterase ACTH activates cells of the adrenal cortex to produce corticosteroids by increasing cAMP (Cyclic Adenosine Monophosphate) (Guyton & Hall, 2000).

2.4. *Interferon gamma (IFN- γ)*

Interferon gamma (IFN- γ) is a multifunctional protein, was first discovered as an antiviral activity in human leukocyte cultures infected by Sindbis virus stimulated by PHA. Produced by T lymphocytes and NK cells. IFN- γ is now known as inhibitors of viral replication and regulation of a number of immunological functions. IFN- γ human is 143 amino acid residues, 20 and 25 kda glycoprotein which is shown as a small bridge homologous with IFN- α and β . Naturally the occurrence of IFN- γ is found as two molecular weight species, divided into levels of glycosylation. IFN- γ produced by CD8 +, NK and Th1 T helper cells. According to the function produces a variety of effects, IFN- γ is stored as the effect of antiviral, antiprotozoal and immunomodulators in apoptotic cell proliferation. Antiprotozoal activity of IFN- γ against Toxoplasma and chlamidia believed to result from the activity of indoleamine 2,3 dioxygenase, an enzyme which is driven by IFN- γ . Immunomodulatory effects of IFN- γ broad and diverse. In monocytes / macrophages, activation of IFN- γ include: increasing the expression of MHC class I antigens and Class II, increasing the production of IL-1, platelet activation factor,

H₂O₂, pterin; protection monocyte not neutrophils. IFN- γ secretion of IgG2a selectively augment B cell stimulation with LPS and IgG3 secretion in T cells is independent type 2 antigens mediated B cell activation. Reported also to spur its own expression. Finally, IFN- γ is known to regulate ICAM-1, but not E-selection or VCAM-1 expression in endothelial cells (Kresno, 2002).

2.5. *The effects of cortisol on immunity*

Glucocorticoids are already widely known to have immunosuppressive effects. But often forgotten that glucocorticoids is an essential requirement for the normal immune response. In animals that undergo adrenalectomy, corticosteroids optimal conditions necessary for normal healing process of infection. In this case the role of the adrenal cortex is greater than the adrenal medulla (Dunn, 1995). Cortisol also lowers eosophil in circulation, so limfopeni and netropeni an important diagnostic criterion overproduction of cortisol by the adrenal cortex. High cortisol levels lead to atrophy of all lymphoid tissues occurs thereby decreasing the release of T lymphocytes and antibodies that ultimately led to decreased immunity (Guyton & Hall, 2000). Glucocorticoids can also interfere with the distribution of lymphocytes in the body which is important as orchestrator cell immunity against infection (Dunn, 1995). Cortisol acts as a suppressor of protein synthesis, including the synthesis of immunoglobulins, lowering eosophil population, basophils, lymphocytes and macrophages in peripheral blood. High doses of cortisol can lead to atrophy of lymphoid tissue in the thymus, spleen and lymph nodes (McCanne, 1994).

Stress conditions for a few days (Guyton & Hall, 2000) will affect CRH CRH and subsequently affect Th-1 and TH-2 to stimulate the secretion of glucocorticoids and catecholamines and affect the production of certain cytokines. Glucocorticoids regulate important mediator that IFN-gamma, IL-4, IL-10 and IL-12. Glucocorticoids affect the production of cytokines IL-12 and IL-10 produced by monocytes. Glucocorticoids inhibit IL-12, IFN-gamma and IL-2 (North et al., 1998). IL-4 is essential for the development of Th-2 response and IL-12 is important for the development of TH-1 response. Macrophages (macrophages are activated by intracellular bacteria), the products of bacterial lipopolysaccharide (LPS), intracellular parasites is also a source of IL-12 (Goldsby et al., 2000). Mediators IL-12 and IFN-gamma is stimulator Th-1 profile development and suppress Th-2 profile. Barriers to IL-12 and IFN-gamma by glukokortikoid (North et al., 1998), as well as stimulation of the production of IL-4 by glukokortikoid (North et al., 1998; Dhabbar & McEwen., 2001). Will induce a Th-2 profiles and suppress Th-1. Increased glucocorticoid inhibits IL-2, IFN-gamma produced by Th-1 resulting in a shift towards Th-2 type. Catecholamines stimulate IL-10 inhibits IFN-gamma, IL-2 and IL-12 (North et al., 1998). Lymphocytes express the glucocorticoid receptor (GR) and very sensitive to changes in levels of cortisol secretion by the adrenal glands. In the event of ligand binding, GR translocate from the cytoplasm to the nucleus and in the nucleus of the cell binds to specific DNA squence called glucocorticoid-responsive elements (GRES) and modulate gene expression (Jiang & Vacchio, 1998).

2.6. *The concept approach nursing care at home (home care) in patients with ischemic stroke*

Definition and development of Home Care (HC) according Pearlin & Aneshensel (1986) is a healthcare services performed at the patient's home. In America, HC organized began around the 1880s, at which time many patients with infectious disease mortality rates are high. Although at the time it has been widely established hospital of this type, but utilization is still very low, because people prefer home care. This condition develops professionally, so that in 1900 there were 12,000 nurses trained in the entire USA. There are 3 types of nurses today that have different functions, namely: (1) visiting nurses / VN in charge of providing nursing care at home in a poor family. (2) public health nurses; preventifg promotional efforts and to protect public health; and (3) independent practice nurses who perform home nursing care of patients in accordance with their needs (Lerman & Linne, 1993). Changes in the payment system services HC (can be paid through a third party / insurance) and the development of specialization in various medical and nursing services, including the development of Home Health Nursing which is a specialization of Community Health Nursing (Allender & Spradley, 2001). In the UK, HC grow professionally during the mid-19th century, with the beginnings of nursing distric, which was originally started by the nuns who care for the sick poor people at home. Then they began to train women from lower middle class to care for the sick poor, under the supervision of the nuns (Lawton et al., 2000).

3. Methodology

This research study design experiments with a model of the Pre - Post Test Group Design. The control group was given Home Care and treatment group were given Home Care Holistic. Subjects measured biological responses such as Cortisol response, IFN- γ and TNF- α and given questionnaires and observed prior to the intervention (pre-test). Then the intervention of the application of holistic care home for 3 months. Furthermore, the measured biological responses (post-test). After the initial measurement results (pre-test) compared with the results of the final measurement (post-test) to determine the biological differences in ischemic stroke patients before and after the intervention of home care holistically. The sample in this study were all patients with ischemic stroke who had been allowed to go home after hospitalization in space Chrysanthemum A Hospital Dr. Soetomo in 2009 and settled in the city of Surabaya consisting of 40 patients by using probability sampling. Selection of patients must

meet the inclusion criteria, which states are willing to be patient survey respondents, patients with ischemic stroke in the first attack, aged between 35-65 years, not anemic, no clinically malnourished, and resides in the city of Surabaya, East Java, Indonesia. The independent variable is the Home Care Holistic, the dependent variable is the level of cortisol, IFN- γ and TNF- α levels. While the control variables were age, sex, education, occupation, marital status, income and history of the disease (DM / Hypertension). The serum blood specimen handling is done as follows:

1. For IFN- γ examination and TNF- α were given EDTA tube then put 3 cc of blood then mess around for 30 minutes at 1000 \times g and then taken the plasma tube is then inserted and stored in Frezer with temperature $\leq -20^{\circ}\text{C}$.
2. For the examination of serum cortisol. Blood inserted 3°C and then allowed 10 minutes ago troubled 30 minutes after it is saved Frezer with temperature $\leq -20^{\circ}\text{C}$

How to examination Cortisol cytokines, IFN- γ and TNF- α used in quantitative ELISA technique. This reagent is a reagent for research purposes. The examination was conducted in the laboratory of Clinical Pathology, Faculty of Medicine. Airlangga University Hospital. Dr Soetomo. The statistical analysis used in this study were paired sample t-test to examine differences in the levels of cortisol, IFN- γ and TNF- α levels in patients with ischemic stroke who receive homecare holistic model of care with patients who received care homecare and test models Hotteling T to know biological response differences between the groups that received treatment with a holistic model of homecare patients receiving care homecare models.

4. Result and Discussion

4.1. Result

Ischemic stroke patients who are 20 treatment model of home care holistic and 20 patients with ischemic stroke who received home care treatment models, obtained the condition that all 40 patients in the islamic religion and family status (married). The picture of the age of the respondents was as follows: the average age of patients with ischemic stroke who received home care is a holistic model of care was 54.6 years, while the average age of patients with ischemic stroke who received care home model of care, is 54 years old. The majority of ischemic stroke patients were female (52.5%). In patients with ischemic stroke who received home care is a holistic model of care mostly male sex (55%), whereas in patients with ischemic stroke who received home care models are mostly women (60%). Most patients with ischemic stroke junior high school education (47.5%).

In patients with ischemic stroke who received home care holistic care models mostly junior high school education (40%), the same thing also happens in patients with ischemic stroke who received home care models that most of the junior high school education as well, amounting to 55%. Most patients with ischemic stroke to work in the private sector (62.5%), whereas patients with ischemic stroke who received home care holistic care models mostly work in the private sector (60%). Most patients with ischemic stroke have incomes below the average minimum wage (85%). In patients with ischemic stroke who received home care holistic care models mostly have incomes below the average minimum wage (80%), whereas in patients with ischemic stroke who received home care models also have income below the average minimum wage (90%) .

The bulk of ischemic stroke patients do not have a history of hypertension (87.5%). In patients with ischemic stroke who received home care is a holistic model of care is largely a history of diabetes (80%), whereas in patients with ischemic stroke who received home care models also do not have a history of hypertension (95%). The majority of ischemic stroke patients had a history of hypertension (97.5%). In patients with ischemic stroke who received home care holistic care models largely a history of hypertension (95%), whereas in patients with ischemic stroke who received home care models, all (100%) had a history of hypertension.

4.1.1. Differences in levels of cortisol, IFN- γ , TNF- α in patients with ischemic stroke before with after the intervention of home care holistic

Test of difference levels of cortisol, IFN- γ , and TNF- α in patients with ischemic stroke before and after the intervention of home care holistic indicated in Table 4.1.

Table 4.1. Cortisol conditions, IFN- γ and TNF- α ischemic stroke patients before and after treatment, model of home care holistic in the city of Surabaya in 2010

	Before treatment models of home care holistic		After treatment models of home care holistic		Paired t-test	
	mean	SD	mean	SD	Value Stat.	Sign.
Cortisol	10.9400	2.04074	10.0550	1.95272	1.662	0.113
IFN- γ	15.1500	11.68951	14.8200	8.39427	0.172	0.865
TNF- α	9.4950	3.66326	8.1600	3.09913	2.788	0.012

From the table above, it appears that there is a decrease in the average cortisol, IFN- γ and TNF- α ischemic stroke patients after treatment holistic model of home care. To Cortisol, by using a paired t-test significance value of 0.113, which means there is no difference in cortisol before and after ischemic stroke patients receive treatment with a holistic model of home care. The same thing happened in the IFN- γ , by using a paired t-test significance value of 0.865, which means there is no difference in IFN- γ before and after ischemic stroke patients receive treatment with a holistic model of home care. Different things happen in TNF- α , by using a paired t-test significance value of 0.012 which means that there is a difference (downhill) TNF- α before and after ischemic stroke patients receive treatment with a holistic model of home care. Test differences cortisol levels, IFN- γ and TNF- α in patients with ischemic stroke before and after the intervention of home care are shown in Table 4.2.

Table 4.2. Cortisol conditions, IFN- γ and TNF- α ischemic stroke patients before and after treatment models of home care in the city of Surabaya in 2010

	Before treatment models of home care		Before treatment models of home care		Paired t-test	
	mean	SD	mean	SD	Value Stat.	Sign.
Cortisol	8.5450	2.72367	9.3000	2.46875	-1,134	0,271
IFN- γ	13.8400	5.15766	15.3950	7.87143	-1,160	0,260
TNF- α	5.7200	2.62911	8.4350	4.25568	-4,607	0,000

From the table above, it appears that there was an average increase of cortisol, IFN- γ and TNF- α ischemic stroke patients after treatment models of home care. To Cortisol, using paired t-test significance value of 0.271, which means there is no difference in cortisol before and after ischemic stroke patients receive treatment with a model home care. The same thing happened in the IFN- γ , using paired t-test significance value of 0.26, which means there is no difference in IFN- γ before and after ischemic stroke patients receive treatment with a model home care. Different things happen in TNF- α , using paired t-test significance value of 0.0 which means that there is a difference (increase) TNF- α before and after ischemic stroke patients receive treatment with a model home care.

4.1.2. Differences in levels of cortisol, IFN- γ and TNF- α in patients with ischemic stroke who received care home model of care than those who received treatment with a model of home care holistic

The results of the analysis on the levels of cortisol, IFN- γ and TNF- α in ischemic stroke patients before treatment holistic model of home care and nursing home care models are shown in Table 4.3.

Tabel 4.3. Cortisol conditions, IFN- γ and TNF- α ischemic stroke patients before treatment model of home care holistic and home care models in Surabaya in 2010

Before treatment	Treatment groups model of home care holistic		Treatment groups model of home care		Paired t-test	
	mean	SD	mean	SD	Value Stat.	Sign.
Cortisol	10.9400	2.04074	8.5450	2.72367	3.147	0.003
IFN- γ	15.1500	11.68951	13.8400	5.15766	0.459	0.649
TNF- α	9.4950	3.66326	5.7200	2.62911	3.744	0.001

From the table above, it appears that the average cortisol ischemic stroke patients prior to treatment holistic model of home care at 10.94, while the average cortisol ischemic stroke patients before the treatment model of home care by 8.545. By using t-test significance value of 0.003 which means that there are differences in cortisol prior ischemic stroke patients who received treatment with a model of home care holistic and home care models.

On average IFN- γ ischemic stroke patients prior to treatment holistic model of home care at 15.15, while the average IFN- γ ischemic stroke patients before the treatment model of home care for 13.84. By using t-test significance value of 0.649, which means there is no difference in IFN- γ prior ischemic stroke patients who received treatment with a model of home care holistic and home care models.

On average TNF- α ischemic stroke patients prior to treatment holistic model of home care at 9.495, while the average TNF- α ischemic stroke patients prior to treatment home care models of 5.72. By using t-test significance value of 0.001 which means that there are differences in TNF- α prior ischemic stroke patients receive treatment with a model of home care holistic and home care models. Because there are differences in cortisol and TNF- α prior to treatment, then to see the effect of holistic nursing home care models and models of home care will be used margin decline in cortisol, IFN- γ and TNF- α . The picture cortisol, IFN- γ and TNF- α after treatment are as follows:

Table 4.4. Cortisol conditions, IFN- γ and TNF- α ischemic stroke patients after treatment model of home care holistic and home care models in Surabaya in 2010

After treatment	Treatment groups model of home care holistic		Treatment groups model of home care	
	mean	SD	mean	SD
Cortisol	10.0550	1.95272	9.3000	2.46875
IFN- γ	14.8200	8.39427	15.3950	7.87143
TNF- α	8.1600	3.09913	8.43500	4.25568

From the table above, it appears that there is a decrease in cortisol levels, IFN- γ and TNF- α for ischemic stroke patients who receive care model of home care holistic and home care models. But statistical analysis will be performed to see the effect of care model by using the difference (decrease) cortisol, IFN- γ and TNF- α , after obtaining the care model.

The results obtained by analysis of the difference / decrease in cortisol, IFN- γ and TNF- α in ischemic stroke patients before and after treatment model of home care holistic and nursing home care models are shown in Table 4.5.

Table 4.5. Cortisol excess conditions, IFN- γ and TNF- α ischemic stroke patients who received home care holistic models and models of home care in the city of Surabaya in 2010

Difference (Decrease)	Treatment groups model of home care holistic		Treatment groups model of home care		Paired t-test	
	mean	SD	mean	mean	SD	mean
Cortisol	0.8850	2.38157	-0.7550	2.97666	1.924	0.062
IFN- γ	0.3300	8.56339	-1.5550	5.99495	0.806	0.425
TNF- α	1.3350	2.14164	-2.7150	2.63524	5.334	0.000

From the table above it appears that, there is a decrease in cortisol, IFN- γ and TNF- α in patients with ischemic stroke after treatment holistic model of home care, whereas in patients with ischemic stroke who received care home model of care does not decrease, even an increase. In cortisol, decreased by an average of 0.885 after treatment holistic model of home care and an increase in cortisol with an average of 0.755 after the model of home care treatment. The decrease or increase in cortisol that occurs is not too large. By using a t-test of significance value of 0.062, which means there is no difference in cortisol difference in ischemic stroke patients who received treatment with a holistic model of home care and home care models.

In IFN- γ , decreased by an average of 0.33 after treatment holistic model of home care and an increase in cortisol with an average of 1.55 after the model of home care treatment. The decrease or increase in IFN- γ is happening is not too big. By using a t-test of significance value of 0.425, which means there is no difference in IFN- γ difference in ischemic stroke patients who received treatment with a holistic model of home care and home care models. In TNF- α , decreased by an average of 1.335 after treatment holistic model of home care and an increase in TNF- α with an average of 2,715 after care home model of care. The decrease or increase in TNF- α happens quite large. By using t-test significance value of 0.00 which means that there are differences in TNF- α difference in ischemic stroke patients who received treatment with a holistic model of home care and home care models. If the difference analysis of cortisol levels, IFN- γ and TNF- α for ischemic stroke patients who receive care holistic model of home care and home care models together (multivariate), the obtained values as follows.

Tabel 4.6. Multivariate and univariate analysis excess cortisol, IFN- γ and TNF- α ischemic stroke patients who received home care holistic models and models of home care in the city of Surabaya in 2010

Difference (Decrease)	Univariate		Multivariate (Hotelling's Trace)		
	F	Sign.	Value	F	Sign.
Cortisol	3,702	0,062	0,858	10,296	0,000
IFN- γ	0,650	0,425			
TNF- α	28,449	0,000			

From the table above it appears that, by using Hotelling's Trace test, significance value of 0.00, which means that there are differences in excess cortisol, IFN- γ and TNF- α in ischemic stroke patients who received treatment with holistic models and models of home care home care. If further analysis to determine the dominant variable that makes the difference difference cortisol, IFN- γ and TNF- α in ischemic stroke patients who received treatment with a holistic model of home care and home care models (in univariate) the results showed that TNF- α is variable that stands out and makes the difference condition ischemic stroke patients who received treatment

with a holistic model of home care and home care models with a significance value of 0.00. For cortisol and IFN- γ fact can not be used to indicate a difference in the condition of patients with ischemic stroke who received treatment with a holistic model of home care and home care models with a significance value of 0.065 respectively for cortisol, and 0.425 for IFN- γ .

4.2. Discussion

4.2.1. Differences in levels of cortisol, IFN- γ , TNF- α in patients with ischemic stroke before with after the intervention of home care holistic

Anxiety disorders and depression that continues for a long time and ongoing cause ACTH increases. Increased ACTH can activate the adrenal cortex to secrete gluco-corticoid hormones, particularly cortisol. Cortisol acts as a suppressor of protein synthesis including immunoglobulin synthesis, decrease the number of eosinophils, basophils, lymphocytes and macrophages in peripheral blood.

If immunogen enters the body, the immunogen was captured by macrophages. Then macrophages deliver antigen (immunogen), the T lymphocytes that simultaneously produce and release interleukin 1 (IL-1) is a protein that activates lymphokine-T cell subset, which has a supporting role (T-helper) as well as secreting Th cells IL-2 is a protein that activates T-cell proliferation becomes more. Th cells can activate B-lymphocytes to differentiate into plasma cells (limfositik-B effector). Then plasma cells will produce antibodies against the antigen (immunogen) which enters the immune system. Mechanism of action of cortisol inhibits macrophages to produce IL-1, and Th cells to produce IL-2 cells. It turns will lower cortisol response of Th cells and a decrease in Th cells cause a decrease in cell antibodies by plasma cells (Berne, 1999).

With the intervention of home care is through a holistic approach to the bio-psycho-social-spiritual, coping strategies of patients can do well there will be a condition called adaptive / homeostasis. This is a positive cognitive signals, so as to modulate the immune system. Immune enhancement process workflow is as follows:

First, positive cognitive signals to the brain passes through the sensory system, after reaching the thalamus signal is forwarded to the sensory cortex to be processed and forwarded to the transitional cortex for cognitive control processes next. Furthermore, the signal is projected to be projected onto the amygdala to the hypothalamus. This transmission will lead to a balance between the synthesis and secretion of neurotransmitters.

Second, the balance of synthesis and secretion of neurotransmitters that are inhibitory and eksetasi will influence the secretion of CRF by PVN of the hypothalamus. With uncontrolled CRF secretion of ACTH secretion will be controlled also by the HPA (hypothalamus, pituitary, adrenal) and with controlled secretion of ACTH, will affect the balance of the adrenal cortex to secrete cortisol.

Third, the decline in cortisol levels will act as the body's immune system modulation of both specific and non-specific, cellular and humoral. Decreased cortisol levels will increase levels of CD4 +, so that will differentiate into effector Th1 and Th2 cells. Thus Th1 and Th2 will be more active. On the one hand, Th1 IFN- γ can secrete that increase cellular immunity or macrophages. Macrophages activated by IFN- γ released stimulate Th1 inflammation. On the other hand, Th2 cells can stimulate increased activity B assisted by stimulation of Th1 due to Th2 containing IL-2R and are associated with IL-2 secreted by Th1. IFN- γ secreted Th1 number and activity increases, these cytokines work in B cells and induces active Switching immunoglobulin (Ig) into immunoglobulin G1 (IgG1), an Ig isotype that is closely related to the receptor 23 FCY from the beginning of macrophages, so it can work as a potent opsonin. (Imoboden, 1997), At the same time activated macrophages release several kinds of cytokines TNF- α , among others, which is the main cytokine proinflammatory, so that protein synthesis is not disturbed, good cellular signal an immune response either at each stage there is a release of the body's mechanism to neutralize the called regulators, then there will be no ongoing reaction that can cause widespread tissue damage in ischemic stroke patients. Thus ends the formation of antibodies in the feedback inhibition and created a state of homeostasis.

In this study, there appears to be a decrease in the results of the analysis of average cortisol, IFN- γ and TNF- α ischemic stroke patients after treatment holistic model of home care. For TNF- α , by using a paired t-test P = 0.012 obtained value and the value of t = 2.788, which means there is a difference (downhill) TNF- α before and after ischemic stroke patients who received treatment with a holistic model of home care. This is because in patients with ischemic stroke in the brain tissue, not only neurons are impaired, but a variety of other cells in the brain tissue can also be susceptible to interference which will lead to changes in accordance with the function of every cell. Some immunocompetent cells in the ischemic brain tissue will respond as ischemic stimuli to influence the production of cytokines mediator molecules that form. For each different stimuli, possible responses would be different cytokine production.

Mikrogilia, which is a major source of cytokines in cerebral, in the presence of hypoxia will increase the production of cytokines, IL-1 and TNF- α (Hampel, 1996, Guilan 1997). IL-1 and TNF- α also will trigger limfositik Th-1 where Th-1 also producing IL-1 and TNF- α . Besides, IL-1 and TNF- α have an influence suppression of lymphocyte Th-Th-2 and 3. Ehrlich et al. (1998) suggest that IL-1 beta and TNF- α cytokine classified into proinflammatory. Inflammatory response that followed immediately after the occurrence of ischemic brain tissue

had to be a bad influence on the development of brain tissue infarction (Ferarese et al., 1999; Del Zoppo, 2000; Tuttolomondo et al., 2012). In the inflammatory phase of ischemic stroke patients who suffered damage cells thus causing an increase in macrophage activity, with an increase in macrophages causing inflammatory mediator TNF- α in particular increased. But after the crisis stops decreasing cell damage, inflammatory reactions decreases, so that inflammatory mediators (TNF- α decreases). The occurrence of this can be caused by a reduction of cells damaged by ischemia or brain tissue repair.

For cortisol, using paired t-test $P = 0.113$ obtained value and the value of $t = 1.662$, while for IFN- γ value of $P = 0.865$ and the value of $t = 0.172$, which means there is no difference in cortisol and IFN- γ before and after ischemic stroke patients get care with a holistic model of home care. But statistically cortisol $\bar{x} = 10.94$ before treatment holistic model of home care. The after care home care holistic model of cortisol $\bar{x} = 10.055$. For IFN- γ $\bar{x} = 15.15$ before treatment holistic model of home care. The after care home care holistic model of IFN- γ $\bar{x} = 14.82$. This appears cortisol levels and IFN- γ in a state-regulated

4.2.2. Differences in levels of cortisol, IFN- γ and TNF- α in patients with ischemic stroke who received home care treatment models compared with the model group home care holistic

By the time the patient know that the manifestation of ischemic stroke with paralysis, the face is not symmetrical and speech disturbances, there will be stress psychological, social and spiritual. Excitatory severe stress experienced by patients with ischemic stroke follows the path of the sensory system towards the thalamus. In the thalamus stress stimuli will lead to the sensory cortex and then headed to the amygdala. This situation will affect the immune system. Effect of stress response in immune system function occurs through the hypothalamus and pituitary peptides, ie CRF (corticotropin releasing Factor) and ACTH (adrenocorticotrophic hormone). CRF is the main substance that describe stressor signal to the immune system, resulting CRF HPA axis becomes active, which will include increased ACTH stimulates the cortex adrenaline to increase the secretion of cortisol. In the state of stress in high blood cortisol levels because all leukocytes including lymphocytes have receptors for cortisol cortisol modulates the immune system (Dunn, 1995; Tache et al., 1999; Otagiri et al., 2000) that high cortisol levels are immunosuppressor (Dunn, 1995) so that the CD4 suppresses by cortisol become less active and less active CD4 cells differentiate into TH1, TH2 and TH3 were also less active. TH1 cells secrete IL-2, IL-2 then binds to the IL-2R produced by TH2, so TH2 activity also decreases, and TH2-stimulated B cells, because TH2 is less active, less active B cells, resulting in the production of immunoglobulin by cell Breakfast is not much. TH1 cells whose activity decreased, remained secrete IFN- γ that amount and aktiifitasnya also declined. So that macrophages are activated by IFN- γ activity will decline. Decreased macrophage activity will result in the release of cytokines such as TNF- α macrophages, IL-1, IL-6, IL-8, IL-12 and TGF- β 1 activity also decreased. TH3 cells which didiferensiasi of CD4 as mainstreaming activities also decreased cortisol suppression of TGF- β 1 thus produced TH3, the amount and activity decreased to reflect the shape of the relationship depicted in the flow of thought, the resulting decrease in cytokine-mediated immune response is not optimal.

In this study, patients receiving home care is a holistic model of care experienced learning process menghasilkan positive cognition. These circumstances lead to modulation of the immune response, namely CD4. increase in CD4 levels will increase inter-cell avidity binding to the appropriate MHC on the surface of target cells. In addition, CD4 also have signal transduction to regulate T cell activation through tirosinekinase specific for T cells (Kresno, 2002). Signal diteima of these inflammatory cells induce lymphocytes to produce various types of lymphokines particularly IFN- γ . Increased activation of IFN- γ increases the cytotoxic activity of NK cells in various ways, including increased expression of recognition molecules on the surface of target cells to change the nature of the fluid present in NK cells so that the cells easily attached and meningkatkanproduksi cytolytic molecules to destroy the antigen.

Natural stressors in patients with ischemic stroke is a biological stress which can lead to cell stress. Perception of course patients receive holistic and individualized depending on education, experience and personality of a person's character (Maramis, 2003). Patients who could do with a good coping strategy, there will be a state of the adaptive or homeostasis. The response will trigger biological responses adaptive form of defense cells to stay alive. In this study biological responses that cortisol, IFN- γ and TNF- α there is a decrease in ischemic stroke patients after treatment holistic model of home while on ischemic stroke patients who receive care home model of care does not decrease even increased.

It is suspected in patients with ischemic stroke who undergo a process of inflammation in ischemic brain tissue in the acute phase would maintain the macrophage inflammatory response to the release of IL-1 and Improve neutrofil production and monocytes. TNF- α and IL-1 is a 2 cytokine that plays an important role in the inflammatory response produced by macrophages. Cytokines that increase local endothelial adesilekosit to allow leukocyte chemotactic move according sinyak of chemokines that also produced macrophages. Macrophages also produce cytokines that work on T-cells include IL-1, IL-12 and IL-18. IL-1 is a general activator of T-cells and megaktifkan Th-1 and NK cells that release of TNF- α and TNF- α more.

Acute inflammatory response is controlled by the anti-inflammatory cytokines (IL-4, IL-10 and TGF β). Corticosteroids remembered as an anti-inflammatory and can prevent the production of virtually all

proinflammatory mediators, lowering prevent macrophage activation and synthesis of IFN- γ and TNF- α . The state can suppress inflammation by preventing the proliferation and migration of cells. When the inflammatory phase meolekul already in neutralization by anti-inflammatory, healing begins with a network involving a variety of cells such as fibroblasts and macrophages, which produce collagen which is required by the network.

5. Conclusion

The conclusion of this study is the difference in the levels of cortisol, IFN- γ and TNF- α in patients after ischemic stroke before the homecare holistic intervention. There are differences in excess cortisol, IFN- γ and TNF- α in patients with ischemic stroke who received care home model of care with a holistic model of home care. The suggestion of this research is necessary to further study the effects of Nursing Home Care Holistic models to changes in biological responses to other cytokines, especially IL-2 which protects apoptosis and improve immunity through cytokines.

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